REMARKS

Claims 22-42 are pending in this application and under examination. By amendment above, claims 22, 23, 27, 32, 33, 37 and 38 have been amended. No new matter has been introduced into the claims as a result of these amendments. The additional language inserted into claim 22 is supported by language from the preamble of that claim as originally presented and by the original language of claim 23. The amendments to claim 23 are made to bring the language of that claim into conformance with the amended language of claim 22. Support for the additional language inserted into each of claims 27 and 32 can be found, for example, in paragraphs [0037] - [0039] and in Example 4 of the application. The amendments to claim 33 are made to bring the language of that claim into conformance with the language of claim 32. The amendments to claim 37 are supported, for example, by claims 41 and 42, and the amendments to claim 38 are made to bring the language of that claim into conformance with the language of claim 37.

All of the pending claims remain rejected under 35 U.S.C. § 103(a) as unpatentable over Myers et al., U.S. Patent 6,486,172, and Oxenkrug et al. U.S. Patent 6,353,015. The examiner asserted that Myers teaches that nicotine increases cognition and attention and that Oxenkrug teaches that melatonin improves

cognition and protects against neurotoxicity. The examiner asserted that it would have been obvious to combine the teachings of the two references because it would have been expected that the combination of components would treat cognition and memory impairment conditions.

The examiner addressed Applicants' arguments presented in response to the previous Office Action by stating that the Declaration of Dr. Moshe Laudon which was submitted as part of the response was considered to be unpersuasive because (a) Oxenkrug clearly teaches that melatonin improves cognition and protects against neurotoxicity, (b) a reference, newly mentioned, by Jean-Louis teaches that melatonin has effects on cognition in elderly people with mild cognitive impairment and (c) the references employed in the Declaration were not considered since they are not on record.

As an initial point, Applicants apologize for their oversight in not submitting the references discussed in Dr. Laudon's declaration with that declaration. Applicants are submitting copies of the references as well as an IDS with this response.

Although the examiner has asserted that Oxenkrug clearly teaches that melatonin improves cognition and protects against neurotoxicity, this is a significant overstatement of what

Oxenkrug fairly teaches. All that can be learned from the Oxenkrug et al. patent is that administration of melatonin showed cognition-enhancing and neuroprotective properties in animal and cell models of Alzheimer's Disease-type neurodegeneration. Oxenkrug and his co-inventors made this limited conclusion themselves, and the limited testing that they reported does not provide a basis for a reasonable belief that the administration of melatonin will improve sleep quality, cognition or memory in persons undergoing nicotine replacement therapy.

This is especially true in view of numerous examples in the literature that melatonin administration can decrease cognition and memory. Such references are discussed in the Rule 1.132 Declaration submitted by Dr. Moshe Laudon in response to the previous Office Action. As Dr. Laudon explained in his declaration, the examiner's position that melatonin is "known to improve cognition and protect against neurotoxicity" is a significant oversimplification of the effects of melatonin administration to humans. The effects of melatonin administration can vary significantly; a review of the literature on melatonin administration shows that the effects of melatonin on cognition, memory and/or sleep are unpredictable: sometimes it appears to be useful, as in the reference cited by the examiner, in other instances it either has no effect or it impairs

cognition, memory and/or sleep. Dr. Laudon cited one reference in which the administration of melatonin appeared to have no effects on cognition or memory and a number of references in which melatonin administration impaired cognition and memory. Thus, the effects of melatonin can vary.

Thus, the limited conclusion that one of skill in the art properly can draw from the Oxenkrug reference, taken in combination with the teachings of the Myers reference is wholly insufficient to render obvious the present invention. A person of skill in the art who read each of these references would have no inclination to consider the teachings of the two references in combination, and even if he were to do so, he would not be lead to the present invention.

As noted above, in commenting on the arguments Applicants submitted in their response to the previous Office Action, the examiner mentioned a paper by Jean Louis, which discusses the results of a study in which melatonin was found to affect cognition in elderly patients with mild cognitive impairment. Applicants note that the melatonin was administered in an immediate release form to a small group of patients and was found to enhance the ability to recall previously learned items but did not affect immediate recall and recognition. There is nothing in the Jean Louis reference, whether taken independently or combined

with the two references which form the basis for the outstanding rejection, which would lead one to the compositions and methods of the claims of the present application.

Specifically, independent claim 22 is directed to a product comprising a first active ingredient selected from melatonin or an agonist or antagonist thereof and a second ingredient selected from nicotine or a nicotine receptor agonist, wherein the first ingredient is provided in a controlled released form in an insomnia-treating effective amount and the second ingredient is provided in the form of a transdermal patch. The combination of the cited Oxenkrug and Myers references does not suggest such a combination. Myers teaches only that nicotine can increase attention span and cognition in humans. The shortcomings of Oxenkrug are discussed above; Oxenkrug's limited teaching that the administration of melatonin showed cognition-enhancing and neuroprotective properties in animal and cell models of Alzheimer's Disease-type neurodegeneration, whether taken alone or in combination with Myers, does not lead one to the product of claim 22, wherein a controlled release form of melatonin is provided in an amount effective for treating insomnia and in combination with a transdermal nicotine patch. The Jean Louis reference, which was mentioned by the examiner but not formally

made a part of the ground of rejection, does not compensate for the deficiencies of the cited references.

Independent claim 27 is directed to a method of treating a patient in the course of nicotine replacement therapy to alleviate one or more adverse effects of nicotine withdrawal through the administration of melatonin or a melatonin agonist or antagonist and nicotine or a nicotine receptor agonist. The cited references do not suggest that melatonin can be administered to one who is receiving nicotine or a nicotine receptor agonist as nicotine replacement therapy to treat the impairment of sleep quality, cognition or memory which is an adverse effect of tobacco withdrawal. Applicants note that with regard to this claim, the examiner had stated that Applicants' previous argument was not persuasive because the claim did not recite that the adverse effect was due to nicotine withdrawal; that now has been made explicit in the claim.

Independent claim 32 is directed to a method of treatment of impairment of sleep quality, cognition or memory through the administration of melatonin or a melatonin agonist or antagonist in controlled, sustained or prolonged release form and optionally in combination with a transdermal nicotine patch. Again, in view of the very limited teachings of Oxenkrug, the combination of Oxenkrug and Myers does not suggest such a form of treatment, and

the teachings of Jean Louis do not compensate for the deficiencies of the two cited references.

Finally, independent claim 37 is directed to a kit comprising a first pharmaceutical formulation comprising melatonin or a melatonin agonist or antagonist in a controlled, sustained or prolonged release form and provided in an amount sufficient to control insomnia, a second pharmaceutical formulation comprising nicotine or a nicotine receptor agonist adapted for transdermal administration. There is no suggestion in Oxenkrug and Myers of a kit comprising such components or that melatonin can control insomnia in patients receiving nicotine replacement therapy. Again, if the Jean Louis reference is added to the others, the combined teachings of the three references do not lead one to the claimed kit.

Applicants respectfully submit that in view of the above amendments and discussion, the pending claims are in condition for allowance.

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